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Predictive factors and pattern of central lymph node metastasis in unilateral papillary thyroid carcinoma

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ABSTRACT

Objective: Prophylactic central neck dissection (CND) for papillary thyroid carcinoma (PTC) remains controversial. The aim of this study was to evaluate the patterns and predictive factors of central lymph node metastasis in cases of PTC that were clinically determined to be node negative.
Methods: We studied 485 patients who have unilateral PTC without clinical lymph node metastasis and underwent total thyroidectomy and prophylactic bilateral CND from 2003 to 2012, retrospectively. The frequency, subsite and predictive factors of central lymph node metastasis were analyzed.
Results: In total, 166 (32.4%) patients had occult central lymph node metastases. The most common subsite of central node metastases was the ipsilateral paratracheal lymph node (26.0%), followed by pretracheal (12.5%), prelaryngeal (5.0%), and contralateral paratracheal (3.9%) lymph nodes. The tumor size larger than 0.5 cm ($p = 0.003$), age under 45 ($p < 0.001$) and extrathyroidal extension ($p = 0.028$) were associated with ipsilateral central compartment metastasis in multivariate analysis. Contralateral central node metastasis was associated with tumor size >3 cm, age under 45, and multifocality and ipsilateral central node metastasis in univariate analysis, but it was associated with only ipsilateral central node metastasis in multivariate analysis ($p = 0.001$).
Conclusion: Prophylactic CND might be considered for PTC patients with large tumor size or extrathyroidal extension based on rates of lymph node metastasis. Unilateral CND might be appropriate as prophylactic CND due to the low metastatic rate to the contralateral paratracheal node.

1. Introduction

Papillary thyroid carcinoma (PTC) generally exhibits an indolent clinical course, but it frequently metastasizes to regional lymph nodes. Although skip metastasis to the lateral compartment may occur, initial nodal metastasis usually occurs in the central compartment. Cervical lymph node metastasis, including micrometastasis, is reported in 20–90% of patients with PTC, and clinically detectable macrometastatic lymph nodes are found in up to 35% of patients [1–4].

There is consensus supporting therapeutic lateral or central neck dissection for clinically apparent lymph node metastasis. Generally prophylactic lateral neck dissection for PTC is not recommended because the impact of microscopic metastasis on recurrence is unclear [5,6]. However, prophylactic central neck dissection (CND) remains controversial because of lack of substantial evidence on the benefit and potential morbidity of the procedure. There is no reliable non-invasive method for detecting cervical lymph node metastasis. The detection of central lymph node metastasis using palpation and imaging studies such as high resolution ultrasonography (US) and computed tomography (CT) is difficult, while the detection of lateral lymph node metastasis is relatively easier. The sensitivity of detecting central compartment lymph node metastasis by US is reported to range from 10% to 53% [7,8]. Additionally, due to its low sensitivity and specificity, intraoperative determination of central lymph node metastasis by the surgeon is a limited guide for CND in clinically node-negative PTC [9]. Sentinel lymph node biopsy for the central compartment is also limited in its ability to accurately guide CND [10,11]. Thus, many authors have advocated the necessity of prophylactic CND in clinically node-negative PTC, although this suggestion remains controversial.

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Therefore, the predictive factors and patterns of occult central lymph node metastasis in PTC must be determined in order to provide indications for prophylactic CND in PTC. Although there have been several reports about predisposing factors and patterns of lymph node metastasis in PTC, the results differ greatly. The aim of this study was to evaluate the patterns and predictive factors of central lymph node metastasis in cases of PTC that were clinically determined to be node negative and, if possible, to suggest the indications and extent of prophylactic CND based on the pattern and incidence of metastasis.

2. Patients and methods

We retrospectively reviewed 485 patients with unilateral PTC who underwent total thyroidectomy with prophylactic CND between January 2003 and December 2012. All patients were diagnosed with PTC or suspicious PTC on preoperative fine needle aspiration cytology (FNAC) and had no cervical lymph node metastasis in preoperative evaluation including physical examination, US, CT, and FNAC. We excluded patients who had bilateral tumors, history of previous thyroid surgery, or incidental PTC after surgery for benign thyroid lesions. The patients who had clinically suspicious metastatic node on preoperative evaluation or who had received lobectomy or thyroidectomy without CND were also excluded.

All patients underwent total thyroidectomy and bilateral CND. All patients were pathologically confirmed to have unilateral PTC after thyroidectomy. During the operation, all parathyroid glands were identified and preserved prior to CND if possible. After bilateral CND, the central compartment lymph node specimen was divided into four subsites and sent to the pathology department. The subsites included ipsilateral and contralateral paratracheal groups, a pretracheal group, and a prelaryngeal group.

We investigated the frequency of occult central lymph node metastasis and distribution of metastasis within the subsites. Analysis of subsite metastasis was performed in 361 patients, excluding 124 patients in whom the central lymph node specimen was not divided into four subsites.

We analyzed predictive factors for central compartment lymph node metastasis including age, gender, tumor size, extrathyroidal extension (ETE), multifocality and lymphovascular invasion. Logistic regression analysis was performed for multivariate analysis in order to determine predictive factors associated with lymph node metastasis. All statistical data were determined using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered statistically significant.

3. Results

Clinicopathologic characteristics and incidence of lymph node metastasis are summarized in Table 1. The study population consisted of 398 females and 87 males, and mean age was 48.6 ± 12.4 years. The mean size of the largest primary tumors was 10.7 ± 8.0 mm. Multifocal tumors were found in 54 patients (11.1%). Extrathyroidal extension was found in 165 patients (34.0%), and lymphovascular invasion was found in 86 patients (17.7%). According to the American Joint Committee on Cancer (AJCC) Staging System (7th edition), T1, T2, T3 and T4 were 294 (60.6%), 23 (4.8%), 161 (33.2%) and 7 (1.4%), respectively, and there was no case with distant metastasis.

The mean number of lymph nodes removed was 6.2 ± 5.6, and the mean number of metastatic lymph nodes was 2.6 ± 2.9. Occult central compartment lymph node metastasis was found in 157 patients (32.4%).

Mean operation time was 152.5 ± 38.2 min, and the mean volume of drainage was 96.4 ± 31.7 ml. Radioactive iodine (RAI) ablation was performed in 415 patients (84.9%). Transient and permanent vocal cord palsy occurred in 26 (5.4%) and two (0.4%) patients, respectively, while transient and permanent hypoparathyroidism occurred in 176 (36.3%) and 12 (2.5%) patients, respectively. Postoperative hematoma occurred in 11 (2.3%) patients, but all cases except two exploratory cases were managed by conservative treatment, such as compression dressing.

On trend testing, ETE, lymphovascular invasion, number of metastatic lymph nodes, and rate of occult lymph node metastasis increased with increasing tumor size. Patients were divided into the following five groups of tumor size: ≤5 mm, 6–10 mm, 11–20 mm, 21–30 mm, and >30 mm. We analyzed the risk of central lymph node metastasis in each group. The mean number of removed lymph nodes did not differ significantly among groups. When compared to the immediate smaller size group, the odds ratio (OR) and 95% confidence interval (CI) of 6–10 mm, 11–20 mm, 21–30 mm, and larger than 30 mm groups were 1.85 (95% CI = 1.10–3.12), 1.64 (95% CI = 0.99–2.70), 0.94 (95% CI = 0.46–1.89), and 7.22 (95% CI = 0.41–36.96), respectively (Table 2).

On univariate analysis, tumor size (>0.5 cm), age younger than 45 years, ETE and lymphovascular invasion were correlated with central lymph node metastasis. However, on multivariate analysis, only tumor size, age, and ETE were correlated with central lymph node metastasis (Table 3).

The patterns of central lymph node metastasis are summarized in Table 4. Central lymph node metastasis most frequently occurred in the ipsilateral paratracheal node (26.0%), followed by the pretracheal group (12.5%), the prelaryngeal node (5.0%), and the contralateral paratracheal lymph node group (3.9%). In 14 (3.9%) patients who had contralateral paratracheal lymph node metastasis, 13 exhibited bilateral metastasis. On stratification analysis according to tumor size, the order of incidence of lymph node metastasis did not change.

Contralateral paratracheal lymph node metastasis correlated with tumor size greater than 3 cm, age younger than 45 years, and

Table 1
Clinicopathologic characteristics of patients with clinically node-negative papillary thyroid carcinoma.

Characteristics	Total (n = 485)	Groups according to tumor size					
		≤0.5 cm (n = 158)	0.5–1 cm (n = 151)	1–2 cm (n = 120)	2–3 cm (n = 44)	>3 cm (n = 12)	p for trend
Size (mean, mm)	10.7 ± 8.0	3.9 ± 1.0	7.9 ± 1.4	14.8 ± 2.9	26.0 ± 2.9	37.3 ± 4.3	
Age (years)	48.6 ± 12.4	49.8 ± 11.3	49.2 ± 12.1	47.0 ± 13.1	47.9 ± 14.0	41.7 ± 12.8	0.176
<45, n (%)	185 (38.1%)	53 (33.5%)	56 (37.1%)	49 (40.8%)	19 (33.9%)	8 (66.7%)	
≥45, n (%)	300 (61.9%)	105 (66.5%)	95 (64.9%)	71 (59.2%)	25 (66.1%)	4 (33.3%)	
Gender (F:M)	398:87	129:29	124:27	100:20	34:10	11:1	0.874
Multifocality	54 (11.1%)	20 (12.7%)	16 (10.6%)	14 (11.7%)	2 (4.5%)	2 (16.7%)	0.449
ETE	165 (34.0%)	28 (17.7%)	46 (30.5%)	61 (50.8%)	24 (54.5%)	6 (50.0%)	<0.001
Lymphovascular invasion	86 (17.7%)	16 (10.1%)	35 (23.2%)	23 (19.2%)	9 (20.5%)	3 (25.0%)	0.036
Number of removed LNs	6.2 ± 5.6	6.3 ± 5.1	7.2 ± 5.7	7.8 ± 8.3	7.3 ± 5.1	7.7 ± 11.1	0.645
Number of metastatic LNs	2.6 ± 2.9	1.7 ± 1.2	2.2 ± 2.2	2.9 ± 3.3	3.9 ± 4.4	4.1 ± 3.0	0.026
Occult LN metastasis	157 (32.4%)	31 (19.6%)	47 (31.1%)	51 (42.5%)	18 (40.9%)	10 (83.3%)	<0.001

ETE, extrathyroidal extension; LN, lymph node.